Protocol

Autologous Chondrocyte Implantation for Focal Articular Cartilage Lesions

(70148)

Medical Benefit		**Effective Date**: 04/01/16	**Next Review Date**: 01/18
Preauthorization	Yes	**Review Dates**: 02/07, 02/08, 03/09, 01/10, 01/11, 09/11, 09/12, 09/13, 07/14, 07/15, 01/16, 01/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With focal articular cartilage lesions of the knee	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • Symptoms • Functional outcomes • Implant survival • Quality of life • Resource utilization
Individuals: • With focal articular cartilage lesions of joints other than the knee	Interventions of interest are: • Autologous chondrocyte implantation	Comparators of interest are: • Marrow stimulation • Osteochondral autografts	Relevant outcomes include: • Symptoms • Functional outcomes • Implant survival • Quality of life • Resource utilization

Description

A variety of procedures are being developed to resurface articular cartilage defects. Autologous chondrocyte implantation (ACI) involves harvesting chondrocytes from healthy tissue, expanding the cells in vitro, and implanting the expanded cells into the chondral defect under a periosteal or fibrin patch. Second- and third-generation techniques include combinations of autologous chondrocytes, scaffolds, and growth factors.

Summary of Evidence

The evidence for ACI for individuals who have focal articular cartilage lesions of the knee includes randomized controlled trials (RCTs) and prospective observational studies. Relevant outcomes are symptoms, functional outcomes, implant survival, quality of life, and resource utilization. Although evidence from long-term studies is still accumulating, current evidence indicates that Food and Drug Administration–approved ACI products can improve symptoms in some patients with lesions of the articular cartilage of the knee. These patients, who are too young for total knee replacement, have limited options. Therefore, ACI may be considered an option for large disabling full-thickness chondral lesions of the knee caused by acute or repetitive trauma. Evidence indicates that a prior surgical procedure may negatively impact the success of ACI, but ACI combined with meniscal

allograft results in outcomes similar to either procedure performed alone. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence on ACI for individual who have focal articular cartilage lesions in joints other than the knee is limited. Relevant outcomes are symptoms, functional outcomes, implant survival, quality of life, and resource utilization. The greatest amount of literature is for ACI of the talus. A systematic review found that outcomes following treatment with ACI were inferior to microfracture. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Autologous chondrocyte implantation may be considered **medically necessary** for the treatment of disabling full thickness articular cartilage defects of the knee caused by acute or repetitive trauma when all of the following criteria are met:

- Adolescent patients should be skeletally mature with documented closure of growth plates (e.g., 15 years or older). Adult patients should be too young to be considered an appropriate candidate for total knee arthroplasty or other reconstructive knee surgery (e.g., younger than 55 years).
- Focal, full thickness (grade III or IV) unipolar lesions of the patella or the weight bearing surface of the femoral condyles or trochlea at least 1.5 cm^2 in size
- Documented minimal to absent degenerative changes in the surrounding articular cartilage (Outerbridge Grade II or less), and normal-appearing hyaline cartilage surrounding the border of the defect
- Normal knee biomechanics or alignment and stability achieved concurrently with autologous chondrocyte implantation

Autologous chondrocyte implantation for all other joints, including talar, and any indications other than those listed above is considered **investigational**.

Matrix-induced autologous chondrocyte implantation is considered **investigational**.

Policy Guidelines

For smaller lesions (e.g., smaller than 4 cm^2) if debridement is the only prior surgical treatment, then consideration should be given to marrow-stimulating techniques before ACI is performed.

The average defect size reported in the literature is about five cm^2; many studies treated lesions as large as 15 cm^2.

Severe obesity, e.g., body mass index greater than 35 kg/m^2, may affect outcomes due to the increased stress on weight bearing surfaces of the joint.

Misalignment and instability of the joint are contraindications. Therefore, additional procedures, such as repair of ligaments or tendons or creation of an osteotomy for realignment of the joint, may be performed at the same time. In addition, meniscal allograft transplantation may be performed in combination, either concurrently or sequentially, with ACI.

The entire ACI procedure consists of four steps: 1) the initial arthroscopy and biopsy of normal cartilage, 2) culturing of chondrocytes, 3) a separate arthrotomy to create a periosteal flap and implant the chondrocytes, and 4) post-surgical rehabilitation. The initial arthroscopy may be scheduled as a diagnostic procedure; as part of this procedure, a cartilage defect may be identified, prompting biopsy of normal cartilage in anticipation of a

possible chondrocyte transplant. The biopsied material is then sent for culturing and returned to the hospital when the implantation procedure (i.e., arthrotomy) is scheduled.

Background

Damaged articular cartilage typically fails to heal on its own and can be associated with pain, loss of function, and disability and may lead to debilitating osteoarthritis over time. These manifestations can severely impair a patient's activities of daily living and adversely affect quality of life. Conventional treatment options include débridement, subchondral drilling, microfracture, and abrasion arthroplasty. Débridement involves the removal of synovial membrane, osteophytes, loose articular debris, and diseased cartilage and is capable of producing symptomatic relief. Subchondral drilling, microfracture, and abrasion arthroplasty attempt to restore the articular surface by inducing the growth of fibrocartilage into the chondral defect. Compared with the original hyaline cartilage, fibrocartilage has less capability to withstand shock or shearing force and can degenerate over time, often resulting in the return of clinical symptoms. Osteochondral grafts and ACI attempt to regenerate hyaline-like cartilage and thereby restore durable function. Osteochondral grafts for the treatment of articular cartilage defects are discussed in the Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions Protocol.

With ACI, a region of healthy articular cartilage is identified and biopsied through arthroscopy. The tissue is sent to a facility licensed by the U.S. Food and Drug Administration (FDA) where it is minced and enzymatically digested, and the chondrocytes are separated by filtration. The isolated chondrocytes are cultured for 11 to 21 days to expand the cell population, tested, and then shipped back for implantation. With the patient under general anesthesia, an arthrotomy is performed, and the chondral lesion is excised up to the normal surrounding cartilage. A periosteal flap is removed from the proximal medial tibia and sutured to the surrounding rim of normal cartilage. The cultured chondrocytes are then injected beneath the periosteal flap. ACI may be considered more effective for larger lesions than microfracture or osteochondral grafts, but it is technically difficult, requiring two procedures and harvesting of periosteum. In addition, use of the FDA-indicated periosteal cover may result in hypertrophy, as well as donor-site morbidity.

Methods to improve the ACI procedure are being investigated, including the use of a scaffold or matrix-induced autologous chondrocyte implantation (MACI) composed of biocompatible carbohydrates, protein polymers, or synthetics. Desired features of articular cartilage repair procedures are the ability (1) to be implanted easily, (2) to reduce surgical morbidity, (3) not to require harvesting of other tissues, (4) to enhance cell proliferation and maturation, (5) to maintain the phenotype, and (6) to integrate with the surrounding articular tissue. In addition to the potential to improve the formation and distribution of hyaline cartilage, use of a scaffold with MACI eliminates the need for harvesting and suture of a periosteal patch. A scaffold without cells may also support chondrocyte growth.

Regulatory Status

The culturing of chondrocytes is considered by the U.S. FDA to fall into the category of manipulated autologous structural (MAS) cells, which are subject to a biologic licensing requirement. At the present time, only Carticel™ (Aastrom Biosciences) has received FDA approval for the culturing of chondrocytes through a biologics license. In 1997, Carticel received FDA approval for the repair of clinically significant, "...symptomatic cartilaginous defects of the femoral condyle (medial lateral or trochlear) caused by acute or repetitive trauma…." The labeled indication was revised in October 1999 to read as follows:

> "Carticel is indicated for the repair of symptomatic cartilaginous defects of the femoral condyle (medial, lateral, or trochlear), caused by acute or repetitive trauma, in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure."

Thus, the revised labeling suggests a more restricted use of autologous chondrocytes (i.e., as a second-line therapy after failure of initial arthroscopic or surgical repair).

> "Carticel is not indicated for the treatment of cartilage damage associated with osteoarthritis. Carticel should only be used in conjunction with débridement, placement of a periosteal flap and rehabilitation. The independent contributions of the autologous cultured chondrocytes and other components of the therapy to outcome are unknown. Data regarding functional outcomes beyond three years of autologous cultured chondrocyte treatment are limited."

A number of second-generation methods for implanting autologous chondrocytes in a biodegradable matrix are currently in development/testing or are available only outside of the United States. They include Atelocollagen (collagen gel; Koken), Bioseed® C (polymer scaffold; BioTissue Technologies) CaReS (collagen gel; Ars Arthro), Cartilix (polymer hydrogel; Biomet), Chondron (fibrin gel; Sewon Cellontech), Hyalograft C (hyaluronic acid-based scaffold; Fidia Advanced Polymers), MACI® (matrix-induced autologous chondrocyte implantation [ACI]; Aastrom Biosciences, available outside of the United States), NeoCart (ACI with a 3-dimensional chondromatrix; Histogenics, phase 3 trial), and Novocart®3D (collagen-chondroitin sulfate scaffold; Aesculap Biologics, phase 3 trial). ChondroCelect® (characterized chondrocyte implantation; TiGenix; phase 3 trial completed) uses a gene marker profile to determine in vivo cartilage-forming potential and thereby optimizes the phenotype (e.g., hyaline cartilage vs. fibrocartilage) of the tissue produced with each ACI cell batch. Each batch of chondrocytes is graded based on the quantitative gene expression of a selection of positive and negative markers for hyaline cartilage formation. Although clinical use of these second-generation ACI products has been reported in Europe and Asia, none is approved for use in the United States at this time.

Related Protocols

Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

Continuous Passive Motion in the Home Setting

Meniscal Allografts and Other Meniscal Implants

Orthopedic Applications of Stem Cell Therapy (Including Allografts and Bone Substitutes Used With Autologous Bone Marrow)

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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